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Published in:
Mycoses

DOI:
[10.1111/myc.12874](https://doi.org/10.1111/myc.12874)

Publication date:
2019

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Rae, N., Kenny, C., & Muldoon, E. G. (2019). Can Intravenous Antifungal therapy be safely used in the Outpatient Parenteral Antimicrobial Therapy (OPAT) setting? *Mycoses*, 62(3), 196-203.
<https://doi.org/10.1111/myc.12874>

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Article type : Review Article

Can Intravenous Antifungal therapy be safely used in the Outpatient Parenteral Antimicrobial Therapy (OPAT) setting?

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Short title Antifungal therapy in OPAT

Key words OPAT, antifungal, parenteral antifungal therapy, invasive candidosis, patient safety

This is the peer reviewed version of the following article: Rae, N., Kenny, C., & Muldoon, E.G. "Can Intravenous Antifungal therapy be safely used in the Outpatient Parenteral Antimicrobial Therapy (OPAT) setting?", *Mycoses* (2018) which has been published in final form at <https://doi.org/10.1111/myc.12874>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving. This article is protected by copyright. All rights reserved.

Acknowledgements

We would like to thank Dr Riina Rautemaa-Richardson for her time spent reviewing and commenting on this manuscript.

Funding

No funding was received in the preparation of this manuscript

Transparency

All authors declare no conflicts of interest

Synopsis

Outpatient parenteral antimicrobial therapy (OPAT) is an established treatment option for patients with a variety of infections who require a period of intravenous therapy, are clinically stable, and do not require continuous monitoring. Many patients with fungal infections require prolonged therapy due to resistance or intolerance to oral antifungal agents. Despite the widespread use of OPAT by infection specialists, antifungal agents appear infrequently used in this setting. We suggest that with appropriate patient selection, patients with fungal infections could successfully be treated on OPAT.

Introduction

Outpatient parenteral antimicrobial therapy (OPAT), the administration of intravenous antimicrobials to patients in the ambulatory setting, has become established as a suitable alternative to inpatient therapy in appropriate patients [1, 2]. Generally, patients selected for OPAT require a period of several days to weeks of parenteral therapy for infections while remaining otherwise well, and fit for discharge from hospital [1]. Infections frequently treated via OPAT services include skin and soft tissue infections, deep-seated infections (including osteoarticular and endovascular infections) and infections caused by resistant organisms where oral therapy is not possible (e.g. in the treatment of infection caused by Extended Spectrum Beta-Lactamase producing organisms). The delivery of OPAT to patients varies widely; it may be delivered in the hospital setting, outpatient or ambulatory care clinics, or by administration at home by community nurses, carers or by patient self-administration. There is a growing body of evidence that OPAT is both safe and cost effective for a wide variety of infections [3], however while there is extensive experience of OPAT with

antibacterial agents, there is a paucity of evidence regarding the use of parenteral antifungal agents in OPAT programmes.

Fungal infections requiring prolonged antimicrobial therapy (such as candidiasis, aspergillosis, cryptococcosis) are more likely to occur in patients with underlying co-morbidities, including immune compromise or other significant co-morbidities such as severe pulmonary disease, diabetes, or malignancy. Traditionally OPAT has not been selected for such patients, and this may account for the low rates of reported use of amphotericin B in the OPAT setting among infectious diseases physicians in the United States and Ireland; 47% and 14% respectively reported experience of using amphotericin B in OPAT [4, 5]. In many patients, therapy with triazole antifungals, which are available as oral agents, is the preferred treatment option; however, in certain circumstances the triazoles may not be appropriate due to resistance, toxicity, or drug-drug interactions. Additionally, the toxicity of antifungal agents may be a concern in an outpatient setting, and close monitoring or cautious adjustment of treatment on a frequent basis is required. This may be an additional barrier to OPAT in this patient cohort, particularly in less well-resourced OPAT programmes. The provision of parenteral antifungal therapy is possible in the OPAT setting provided there is careful and considered patient selection and appropriate safety monitoring and follow-up with an infection specialist is implemented.

Patient Selection & monitoring

The considerations for selecting suitable patients to receive antifungals via OPAT in the first instance are similar to those receiving antibacterial therapy. These factors have been covered extensively elsewhere [1, 2, 6], but in brief the site of infection, identified organism(s), co-morbidities, co-prescribed medications, age, frailty and home circumstances (including home setting, family support and distance from hospital) must all be considered. The recommendation that patients who are considered for OPAT are assessed by clinicians experienced in OPAT is of vital importance in the administration of antifungal agents, given the likely complexity of infection and patient co-morbidity, and potential toxicity of intravenous antifungal agents [1, 2, 6]. We would contend that for antifungal therapy an infection specialist skilled in medical mycology be involved in the decision to discharge a patient on parenteral antifungal therapy (table 1). Additionally, clinicians should also be vigilant for potential drug-drug interactions; utilising on-line antifungal interaction checkers that are available, and pharmacy support to ameliorate such risks [7].

Factors associated with an increased risk of re-admission from OPAT include: infections with resistant organisms, aminoglycoside use, increasing age, and the number of hospital admissions in the last 12 months [8], however factors specific to antifungal agents are unknown. Other evidence suggests that while OPAT in elderly patients is generally safe, re-admission due to de-stabilisation of medical co-morbidities is more common than in their younger counterparts, [9] highlighting that frailty should be a major consideration when assessing suitability for OPAT. These factors are equally, if not more important considerations when selecting patients to receive IV antifungal therapy in the OPAT setting.

Regular clinical review is crucial aspect of patient management on OPAT [1, 2]. The purpose of regular clinical review is to evaluate clinical progress, early detection of adverse events such as those associated with intravascular catheters or side effects or toxicity of administered agent(s) and to determine treatment duration and cessation. Current recommendations are that clinical review is performed weekly by a member of the responsible team, however in certain circumstances longer follow-up duration may be reasonable depending on assessment and clinical judgement. To compliment clinical review, laboratory tests are required to monitor both response to treatment and for toxicity (table 2). Patients require weekly laboratory tests, although for patients receiving amphotericin B twice weekly renal function monitoring is recommended [2]. The review of such laboratory test results by an OPAT clinician has been associated with reduced rates of re-admission [10].

Published studies of patients treated with antibacterial agents on OPAT suggest that readmission rates are between 6 and 31% of episodes, depending on the cohort of patients examined [11-14]. The reasons for readmission vary, with the most frequently reported reasons being complications of therapy, progression of infection, vascular access complications or reasons unrelated to OPAT/ infection being treated. Data relating to readmissions specific to antifungal agents is lacking, however in a small study of patients treated in the community with amphotericin B, 28 of 113 (25%) courses of treatment had to be discontinued and 13 of 113 (12%) courses resulted in hospital admission for nephrotoxicity, vascular access complications or electrolyte disturbances [15].

Antifungal Agents Suitable For OPAT

With regards to antifungal agents that may be administered on OPAT, there are two main options: echinocandins (caspofungin, micafungin or anidulafungin) or liposomal amphotericin B. Oral triazole antifungals, possess good bioavailability, rendering parenteral administration necessary only in exceptional cases. However, significant variability in drug metabolism necessitates therapeutic drug monitoring with the triazoles, and such monitoring could be facilitated through the safety monitoring systems of an OPAT service; enhancing patient safety and optimising outcomes [16].

Echinocandins have broad antifungal activity by inhibition of β -1,3-D-glucan synthesis, with particularly potent fungicidal activity against *Candida spp.* but are fungistatic against *Aspergillus spp.* The three agents have similar once-daily dosing regimens and favourable toxicity profiles compared with amphotericin B [17]. The main adverse effects include infusion reactions, phlebitis, gastrointestinal upset and hepatotoxicity.

Of the three echinocandins, caspofungin undergoes more extensive hepatic metabolism, requiring careful consideration of drug-drug interactions prior to commencing therapy [18]. Known interactions include reduction in serum tacrolimus levels when co-administered with caspofungin, while cyclosporin will increase serum levels of caspofungin. The use of enzyme inducing drugs such as rifampicin, phenytoin, efavirenz, and carbamazepine may reduce serum caspofungin levels. Considerations for the use of micafungin include the potential for hepatotoxicity and gastrointestinal disturbance, the incidence of hepatotoxicity does not appear to differ between caspofungin and micafungin [19]. Less well recognised is the potential for electrolyte disturbances, in particular hyponatraemia that has been described in patients with chronic pulmonary aspergillosis early after the initiation of therapy [20]. Anidulafungin is not metabolised by the liver, so does not have the same propensity for hepatotoxicity and interactions, however hypomagnesaemia, hypokalaemia and headaches are common adverse events. Of the three agents, only micafungin does not require dose loading at the initiation of therapy [19]. A recent small study of patients with chronic pulmonary aspergillosis demonstrated that micafungin could be safely administered via OPAT [21].

The polyene antifungal amphotericin B has been in use for decades. While the agent possesses broad antifungal activity, including *Candida spp.*, *Aspergillus spp.* (excluding *Aspergillus terreus* [22]), Zygomycetes, endemic fungi and *Cryptococcus spp.*, clinical use is often limited by toxicity.

The availability of lipid-based formulations of the drug have essentially replaced amphotericin B deoxycholate and resulted in marked improvement in the drug's safety profile, albeit at increased cost. Adverse effects associated with amphotericin B include infusion-related reactions such as phlebitis, chills, vomiting, arrhythmias, hypotension and bronchospasm [23]. Electrolyte disturbance, nephrotoxicity, and anaemia are commonly reported adverse effects [24]. The risk of nephrotoxicity is increased with use of the deoxycholate preparation versus lipid-based formulations, total cumulative dose, administration of additional nephrotoxic agents and baseline renal dysfunction [25]. It has been postulated that administration of saline prior to infusion of amphotericin B may reduce the risk of nephrotoxicity [26].

Prior to commencing therapy, a test dose is recommended to ensure the patient does not experience a severe hypersensitivity reaction [27]. Pre-treatment with hydrocortisone and chlorphenamine appears to reduce the incidence of infusion related effects [28]. Renal function should be monitored daily on initiation of therapy with amphotericin B [28], meaning that initiation of therapy may be challenging in the OPAT setting, and a period of hospital admission may be required to initiate therapy.

Although there are specific indications for these agents, they are often used as second line therapy when patients cannot receive triazole therapy due to intolerance or resistance [18, 29]. Recent expert opinion on the management of triazole resistant *Aspergillus fumigatus* recommend therapy with either liposomal amphotericin B or an echinocandin combined with voriconazole [30]. With triazole resistance in *Aspergillus fumigatus* increasing worldwide [31], it is likely that an increasing number of patients requiring treatment will have to receive parenteral therapy instead of an oral triazole agent.

Infections caused by *Candida* spp.

Invasive candidiasis (IC) is the most common invasive fungal infection in the developed world and has strong associations with medical intervention, in particular central venous catheters, recent (most commonly intra-abdominal) surgery and broad-spectrum antimicrobial use [32]. The incidence of IC is increasing, [33, 34] and is particularly common in critical care environments. The epidemiology will differ depending on the patient cohort treated, trends of antifungal use, and geographically [35]. With the increased use of fluconazole, the incidence of inherently fluconazole resistant spp. such as *C. glabrata* and *C. krusei* increases [36, 37]. Additionally, echinocandin resistance is now recognised to occur, and is as high as 12% of *Candida* spp. in some series[38]. The emergence of multi-drug resistant *Candida* spp. such as *Candida auris* will add to the challenge of treating IC, and may increase the need to consider OPAT in the treatment of these patients [39].

Obtaining a microbiological diagnosis in invasive candidosis can be difficult, with sensitivity of blood cultures being estimated at approximately 50% in patients with invasive candidiasis [40]. While antimicrobial resistance in community-acquired *Candida* spp. infections is uncommon, triazole resistance is more commonly found in nosocomial isolates. Triazole resistance has implications for the choice of therapy, as invasive infections with resistant strains will require parenteral therapy with an echinocandin or liposomal amphotericin B for the duration of treatment required. This could be facilitated through an OPAT service once the patient is deemed clinically stable and fit for hospital discharge.

Echinocandins have demonstrated superiority in the management of candidaemia, in particular in critically ill patients, and as such are recommended as first line therapy [41, 42]. Many patients with infections caused by species such as *Candida albicans* which are generally susceptible to fluconazole can be de-escalated to oral fluconazole for ongoing therapy once clinically stable and blood cultures on treatment are negative [29, 43]. The current recommendation is 10 days of IV echinocandin prior to de-escalation to fluconazole. Echinocandins should generally not be used in infections caused by *C. parapsilosis* due to theoretical concerns of risk of treatment failure based on the increased MICs to echinocandins exhibited by this species [29].

With the recent identification of *Candida auris* as a worldwide cause of multi-drug resistant outbreaks, increasing use of parenteral antifungal agents in the treatment of *Candida spp.* infections appears likely, and the traditional oral stepdown to fluconazole may not be a therapeutic option [39].

Candida spp. infections that would be particularly suited to OPAT would be uncomplicated candidaemia and deep-seated infections such as osteoarticular or endovascular infections. Patients with candidaemia are at risk of disseminated disease. As a result, all patients with candidaemia should be evaluated for endophthalmitis and endocarditis. Dilated retinal examination should be undertaken to exclude ocular involvement [29]. Surveillance blood culture monitoring is required to ensure candidaemia has been successfully cleared with parenteral antifungal therapy. Echocardiography should be undertaken to assess for endocarditis. Following clearance of blood cultures, patients with uncomplicated candidaemia require 14 days of therapy [29, 43]. This is likely to necessitate inpatient therapy initially but if stable patients could rapidly be transitioned to care on OPAT to complete their therapy.

Candida endocarditis and osteoarticular infections require prolonged therapy, usually in combination with surgery [29, 43]. Following a period of inpatient therapy, when stable these patients could be suitable for treatment via OPAT following surgical intervention. While triazoles show poor penetration into biofilms and vegetations, liposomal amphotericin B and echinocandins exhibit better activity against biofilms associated with *Candida spp.*[44]. These infections require collaboration with surgical colleagues to ensure adequate source control is undertaken; in patients with endocarditis, valve replacement should be pursued, while in septic arthritis surgical drainage should be performed [29]. Assuming there is clearance of bloodstream infection and the patient is stable, therapy can often be de-escalated to an oral triazole in patients with infections caused by susceptible *Candida* isolates, although in non-susceptible isolates parenteral echinocandin or liposomal amphotericin B could be delivered via OPAT.

Chronic hepatosplenic candidiasis also requires prolonged antifungal therapy until there is resolution on imaging, often for months. Initial therapy for the first few weeks should be with an echinocandin or liposomal amphotericin B before stepping down to oral fluconazole if the isolate is fluconazole susceptible, or if the risk of fluconazole resistance is deemed to be low [29].

The spectrum of infections caused by *Candida spp.* is diverse but many patients could be considered for OPAT early in the course of their illness if clinically stable, investigations for metastatic disease have been carried out, and are otherwise fit for discharge. Echinocandins remain the initial therapy of choice for invasive infections, with current recommendations stating therapy should be continued for a minimum of 10 days before switch to oral azole is considered where appropriate [43]. In patients with complicated disease or resistant isolates, where oral therapy may not be an option, therapy on OPAT should be pursued if stable.

Infections caused by *Aspergillus spp.*

Infections caused by *Aspergillus spp.*, including invasive aspergillosis (IA), chronic pulmonary aspergillosis (CPA) and osteoarticular infections may be amenable to therapy with OPAT. Due to underlying comorbidities, patients with IA are likely to require stabilisation with inpatient therapy prior to consideration of discharge, whereas patients with CPA are more likely to be ambulant [45]. While triazoles remain as first line therapy for infections due to *Aspergillus spp.*, liposomal Amphotericin B and echinocandins may be used for a variety of reasons, including azole intolerance, resistance or salvage therapy [18, 46]. Resistant *Aspergillus spp.* can be acquired from the environment, or arise due to previous triazole exposure, and patterns of resistance may differ [47]. The risks for the development of resistance while on triazole therapy include; the burden of *Aspergillus* infection, subtherapeutic serum triazole levels, and patient nonadherence [45]. Triazole resistance has been increasingly identified in *Aspergillus fumigatus*, particularly in Europe. The prevalence of triazole resistance in *A. fumigatus* is approx. 3.2% with some European countries reporting resistance rates as high as 26%[48]. Mutations in the *cyp51A* gene which encodes fungal lanosterol 14a-demethylase, the target of azoles, has led to the development of pan-azole resistant *A. fumigatus* isolates[47].

It should be noted that while the echinocandins may be used as salvage therapy, they are not recommended as monotherapy in the primary treatment of IA [18, 46].

The duration of therapy for *Aspergillus* infection is dependent on the indication. While patients with IA generally receive up to 12 weeks of therapy, patients with CPA often receive prolonged triazole therapy lasting 6 months or more [18, 46]. When parenteral therapy is considered in CPA patients,

short courses of up to 6 weeks or intermittent therapy may be attempted [46]. In patients with CPA, short course (2-4 weeks) micafungin is equivalent to voriconazole, with a favourable side effect profile [49]. Caspofungin and micafungin appear equivalent in improving the health status of patients with CPA [50]. In a small series of patients with sarcoidosis and progressive CPA, cyclical caspofungin resulted in stabilisation of radiological appearance and lung function [51]. A retrospective study of intravenous liposomal amphotericin B in CPA demonstrated high response rates (76.6% for repeated courses <6 weeks duration), but increased risk of acute kidney injury with repeated courses of therapy [52]. In general, the use of parenteral therapy in CPA should be reserved for patients with progressive disease, triazole resistance, and/or those who fail or are intolerant of triazoles [46].

Infections caused by endemic fungi

The so-called endemic mycoses are a diverse group of dimorphic fungi, including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis* and *Talaromyces marneffe* (formerly known as *Penicillium marneffe*). Varying in severity from mild and self-limiting to severe life-threatening infections, some are more commonly seen in patients with severe immunocompromise such as advanced HIV infection, particularly histoplasmosis and coccidioidomycosis [53]. The endemic fungi are mainly associated with respiratory infections but can also cause disseminated disease and meningitis. In general, patients with mild or moderate disease are treated with an azole, most commonly itraconazole, but for patients with severe disease amphotericin B is recommended as initial therapy [54]. Duration of therapy is generally a minimum of 2 weeks parenteral therapy before consideration of de-escalation to an oral azole. A recent randomised controlled trial in patients with HIV-associated talaromycosis suggested that induction with amphotericin B for 2 weeks is superior to therapy with itraconazole alone with respect to 6-month mortality and clinical response [55].

Patients with severe manifestations of these infections, necessitating parenteral therapy, are likely to require inpatient initiation of therapy prior to consideration of OPAT. In some patients OPAT may be precluded by the severity of illness, need for supplementary oxygen or acute organ support. Once clinically stable and ambulant, therapy via OPAT could be considered prior to de-escalation to oral therapy.

Infections caused by *Cryptococcus* spp.

Cryptococcus neoformans is the leading cause of fungal meningitis in severely immunocompromised patients, particularly in association with HIV infection, with the largest burden of disease found in Sub-Saharan Africa and South East Asia [56]. Induction therapy with liposomal amphotericin B with oral flucytosine recommended for a minimum of 2 weeks before switching to oral fluconazole, if flucytosine is not included induction therapy is likely to be longer [54]. *Cryptococcus gattii*, once thought to be a subtype of *C. neoformans*, has been associated with CNS and pulmonary manifestations in both immunocompetent and immunocompromised patients; some strains of *C. gattii*, particularly of the VGII molecular type, are associated with reduced susceptibility to fluconazole and may require parenteral therapy [57].

Treatment for Cryptococcosis on OPAT could be considered when the patient is clinically stable and no longer has a requirement for regular lumbar puncture to reduce intracranial pressure. Flucytosine requires close monitoring for myelosuppression with full blood count. While maintenance therapy is usually in the form of fluconazole, an alternative approach is weekly liposomal amphotericin B, particularly in the case of azole intolerance [58].

Mucormycosis

Mucorales can cause aggressive rhino-orbital, pulmonary, cutaneous or disseminated infections in patients with severe immunocompromise, neutropenia or diabetes [59]. The most commonly associated organisms include *Rhizopus*, *Mucor*, *Lichtheimia*, *Cunninghamella* and *Rhizomucor*. Amphotericin B remains the recommended first line therapy, with isavuconazole or posaconazole as alternatives [60, 61]. The optimal duration of therapy is not clear. Patients with rhino-orbital and cutaneous disease require surgical intervention [60]. Those who require ongoing surgical review and debridement should not be considered for OPAT until surgical excision is considered complete. When surgical management is no longer needed, following physiological stabilisation, continuation of therapy with liposomal amphotericin B on OPAT could be considered, provided close follow up with an infection specialist is available.

Infections caused by *Fusarium* spp.

After *Aspergillus* spp, *Fusarium* spp. is the most common pathogenic mould seen in the setting of solid organ transplant recipients or patients with haematological malignancy, usually presenting as persistent fever with evidence of cutaneous or sinopulmonary disease. Voriconazole or amphotericin B should be used in conjunction with surgical debridement, where possible [62]. As with IA and mucormycosis, where localised disease can be surgically excised, OPAT could be considered when surgical debridement is deemed to be complete, immunocompromise has improved and physiological stability has been achieved. After a period of parenteral therapy, patients with fusariosis may be able to transition to oral triazole to continue prolonged treatment, potentially with a period of secondary prophylaxis, such an approach could be successfully managed in the controlled environment of an OPAT service.

Conclusions

With regards to the treatment of fungal infections, OPAT is an underutilised method of delivering therapy. There is a paucity of clinical experience and, as a result, little published data to guide clinicians in practice. The increase in azole resistance, particularly in *Aspergillus* spp., makes it likely that second line therapy with amphotericin B or an echinocandin will become increasingly common. The use of OPAT to deliver parenteral therapy in the treatment of multi-drug resistant *Candida auris*, now identified as an emerging cause of hospital outbreaks, could reduce risk of ongoing nosocomial transmission. While many patients with fungal infections have significant comorbidities, the ability of OPAT to facilitate delivery of treatment in the community should not be overlooked, improving patients' quality of life and providing them with the opportunity to spend more time with family and friends. A carefully selected cohort of patients could benefit from OPAT and this should be considered by clinicians responsible for their care.

Table 1. Patient selection considerations for OPAT

Patient Selection for OPAT	Issues specific to antifungal therapy administered via OPAT
<ul style="list-style-type: none"> • The OPAT clinical lead should devise specific infection-related inclusion and exclusion criteria • The patient must have the ability to understand the concept of OPAT and to comply with proposed treatment • Monitoring whilst on OPAT mandates that the patient have access to weekly outpatient review • The patient must have the ability to self-report an adverse event or a clinical deterioration • Written consent prior to commencing OPAT ensures that the patient understands the potential adverse drug events that may occur on antifungal therapy. 	<ul style="list-style-type: none"> • Enhanced medications reconciliation; focusing particularly on the potential for drug-drug interactions e.g. with warfarin. • Enhanced monitoring; ensuring there is a method to monitor for potential electrolyte disturbances and nephrotoxicity, particularly early in the course of therapy. • First dose administration; ensuring a system is in place to administer first doses of intravenous antifungals in a healthcare setting due to the potential for infusion reactions. • Outpatient management provided by an infection specialist, skilled in the area of medical mycology.

Table 2. Proposed recommendations for treatment of fungal infections on OPAT

Antifungal	Infection	Follow-up	Monitoring / Considerations
Echinocandins (Caspofungin, micafungin, anidulafungin)	<i>Candida spp.</i> <i>Bloodstream infection</i> (provided blood cultures have cleared) <i>Endocarditis</i> <i>Hepatosplenic candidiasis</i> <i>Osteoarticular infection</i>	Review once / twice weekly	Should not be used for <i>C. parapsilosis</i> Weekly: Full blood count Liver function tests
	<i>Aspergillus spp.</i> <i>Invasive aspergillosis</i> <i>Chronic pulmonary aspergillosis</i> <i>Osteoarticular infection</i>	Review once / twice weekly CPA: Repeat CT thorax in 3-6 months IA: Repeat high-resolution CT after minimum 2 weeks therapy	Weekly: Full blood count Liver function tests
Liposomal Amphotericin B	<i>Candida spp.</i> <i>Bloodstream infection</i> (provided blood cultures have cleared) <i>Endocarditis</i> <i>Hepatosplenic candidiasis</i> <i>Osteoarticular infection</i>	Review once / twice weekly	Twice weekly Renal function Weekly: Full blood count Liver function tests Magnesium
	<i>Aspergillus spp.</i> <i>Invasive aspergillosis</i> <i>Chronic pulmonary aspergillosis</i> <i>Osteoarticular infection</i>	Review once / twice weekly CPA: Repeat CT thorax in 3-	Twice weekly Renal function Weekly: Full blood count

		6 months IA: Repeat high-resolution CT after minimum 2 weeks therapy	Liver function tests Magnesium Should not be used for infections with <i>A. terreus</i> or <i>A. nidulans</i>
	Endemic fungi Pneumonia Disseminated disease	Review once / twice weekly	Consider switch to oral azole after minimum of 14 days therapy Twice weekly Renal function Weekly: Full blood count Liver function tests Magnesium
	<i>Cryptococcus spp.</i> Meningo-encephalitis Disseminated disease	Review twice weekly If recurrence of symptoms: Lumbar puncture / CSF drainage (may need repeated)	Consider switch to oral fluconazole after minimum of 14 days therapy Twice weekly Renal function Weekly: Full blood count Liver function tests Magnesium
	Mucormycosis Rhino-orbital disease Pulmonary disease	Review once / twice weekly	Twice weekly Renal function

	Cutaneous disease Disseminated		Weekly: Full blood count Liver function tests Magnesium
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